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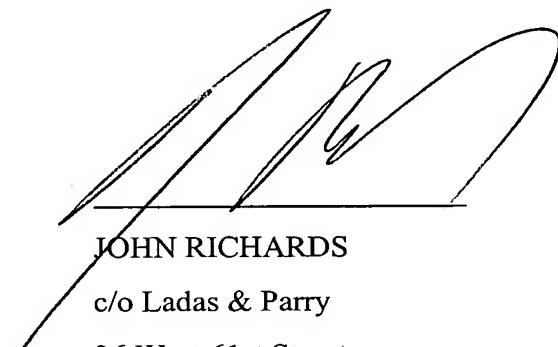
each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷ SO₂NR⁸R⁹, and SO₂R⁷;

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and R⁷, R⁸, R⁹, R¹¹, and R¹² are as defined in Claim 52.

REMARKS

Marked-up copies of claims 16, 17 and 52 are attached as an Appendix

Respectfully submitted,



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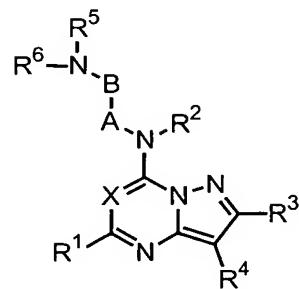
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APPENDIX

16 (Amended) A method of inhibiting the binding of NPY to the NPY1 receptor, which method comprises contacting, in the presence of NPY, a solution comprising a compound of [Claim 1] the formula:



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein:

X is N or CR¹⁴;

R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

R² is H,

C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each of which is optionally substituted with R⁷,

C₃-C₁₀ cycloalkyl, or

(C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; or

R² and R⁶ jointly with the 2 nitrogen atoms to which they are bound, form a C₂-C₅ aminoheterocycle optionally substituted with R⁷, or

R² and A jointly form a C₃-C₆ aminocarbocycle or a C₂-C₅ amino heterocycle optionally substituted at with R⁷;

A represents an alkyl chain of 1,2, or 3 carbon atoms which is optionally mono- or di-substituted at

each carbon with substituents independently selected from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 ; C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 , or
A and B jointly form a C_3 - C_6 carbocycle, optionally substituted at each atom with R^7 ;

B represents an alkyl chain of 1,2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 ; C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 , or

B and R^2 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each atom with R^7 , or

B and R^6 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each atom with R^7 ;

R^3 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 ;

R^4 is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, halogen, C_1 - C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , C_1 - C_6 alkyl- OR^7 , NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, C_1 - C_6 alkyl- $CONR^8R^9$, $COOR^7$, C_1 - C_6 alkyl- $COOR^7$, CN , C_1 - C_6 alkyl- CN , $SO_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is selected from:

C_1 - C_6 alkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1 - C_2 haloalkyl, oxo, OR^7 , cyano, NR^8R^9 , $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7 , $NR^{11}COR^{12}$, $NR^{11}SO_2R^7$.

Aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl(C₅-C₈)cycloalkyl, or heteroaryl(C₅-C₈)cycloalkyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl)C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

C₃-C₁₀ cycloalkyl or C₂-C₉ heterocycloalkyl containing one, two, or three O, S, or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl)C₁-C₆ alkyl, C₁-C₆ alkenyl, oxo, halogen, C₁-C₆ haloalkyl, OR⁷, NR⁸R⁹, (with the proviso that when two OR⁷ or NR⁸R⁹ substituents are geminally located on the same carbon R⁷ is not H and the geminally located OR⁷ or NR⁸R⁹ substituents can be taken together to form a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR⁸R⁹, SO₂R⁷, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl)C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl)C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-

tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo)tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷ SO₂NR⁸R⁹, and SO₂R⁷;

R⁶ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, and SO₂R⁷;

R⁷ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, and SO₂R¹³, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H

R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ amino(heterocycle each of which is optionally substituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;

R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆

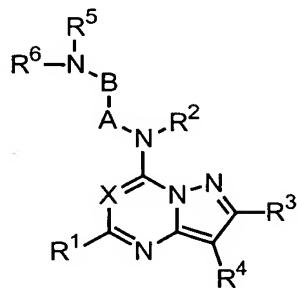
alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H; and

R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN

with cells expressing the NPY1 receptor, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

17. (Amended) A method for altering the signal-transducing activity of a cell surface NPY1 receptor, said method comprising contacting cells expressing such a receptor with a solution comprising a compound of [Claim 1] the formula



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein:

X is N or CR¹⁴:

R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

R² is H,

C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each of which is optionally substituted with R⁷,

C₃-C₁₀ cycloalkyl, or

(C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; or

R² and R⁶ jointly with the 2 nitrogen atoms to which they are bound, form a C₂-C₅ aminoheterocycle optionally substituted with R⁷, or

R² and A jointly form a C₃-C₆ aminocarbocycle or a C₂-C₅ amino heterocycle optionally substituted at with R⁷;

A represents an alkyl chain of 1,2, or 3 carbon atoms which is optionally mono- or di-substituted at each carbon with substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl,

OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹, or
A and B jointly form a C₃-C₆ carbocycle, optionally substituted at each atom with R⁷;

B represents an alkyl chain of 1,2 or 3 carbons atoms, which is optionally mono- or di-substituted
at each carbon with substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl,
(C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl,
OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹, or

B and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each atom with
R⁷, or

B and R⁶ jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each atom with
R⁷:

R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl,
C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹,
C₁-C₆ alkyl-NR⁸R⁹;

R⁴ is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents
independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀
cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, halogen, C₁-C₆ haloalkyl,
trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆
alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl,
heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the
positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole
is substituted;

R⁵ is selected from:

C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is
substituted with 1 to 5 groups independently selected at each occurrence from halo, C₁-C₂
haloalkyl, oxo, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR¹²,
NR¹¹SO₂R⁷;

Aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl(C₅-C₈)cycloalkyl, or heteroaryl(C₅-C₈)cycloalkyl, each
of which is optionally substituted with 1 to 5 substituents independently selected at each

occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

C₃-C₁₀ cycloalkyl or C₂-C₉ heterocycloalkyl containing one, two, or three O, S, or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, oxo, halogen, C₁-C₆ haloalkyl, OR⁷, NR⁸R⁹, (with the proviso that when two OR⁷ or NR⁸R⁹ substituents are geminally located on the same carbon R⁷ is not H and the geminally located OR⁷ or NR⁸R⁹ substituents can be taken together to form a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR⁸R⁹, SO₂R⁷, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring; aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranol, 3-tetrahydrofuranol, 3- or 4-tetrahydrothiopyranol, 3- or 4-(1,1-dioxo) tetrahydrothiopyranol, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl,

quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷ SO₂NR⁸R⁹, and SO₂R⁷;

R⁶ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, and SO₂R⁷;

R⁷ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, and SO₂R¹³, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H

R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each of which is optionally substituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;

R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

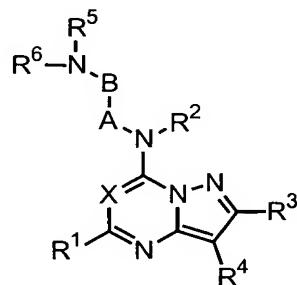
R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H; and

R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN

wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

52 (Amended)

A method of selectively inhibiting binding of NPY, receptors, which comprises contacting a compound of [Claim 1] the formula:



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein:

X is N or CR¹⁴;

R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

R² is H,

C_1 - C_6 alkyl which optionally forms a C_3 - C_6 aminocarbocycle or a C_2 - C_5 aminoheterocycle with A or B, each of which is optionally substituted with R^7 ,

C_3 - C_{10} cycloalkyl, or

(C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl; or

R^2 and R^6 jointly with the 2 nitrogen atoms to which they are bound, form a C_2 - C_5 aminoheterocycle optionally substituted with R^7 , or

R^2 and A jointly form a C_3 - C_6 aminocarbocycle or a C_2 - C_5 amino heterocycle optionally substituted at with R^7 ;

A represents an alkyl chain of 1,2, or 3 carbon atoms which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 ; C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 , or

A and B jointly form a C_3 - C_6 carbocycle, optionally substituted at each atom with R^7 ;

B represents an alkyl chain of 1,2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 ; C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 , or

B and R^2 jointly form a C_3 - C_6 aminocarbocycle , which is optionally substituted at each atom with R^7 , or

B and R^6 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each atom with R^7 ;

R^3 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 .

R^4 is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, halogen, C_1 - C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , C_1 - C_6 alkyl- OR^7 , NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, C_1 - C_6

alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R⁵ is selected from:

C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C₁-C₂ haloalkyl, oxo, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR¹², NR¹¹SO₂R⁷.

Aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl(C₅-C₈)cycloalkyl, or heteroaryl(C₅-C₈)cycloalkyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

C₃-C₁₀ cycloalkyl or C₂-C₉ heterocycloalkyl containing one, two, or three O, S, or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, oxo, halogen, C₁-C₆ haloalkyl, OR⁷, NR⁸R⁹, (with the proviso that when two OR⁷ or NR⁸R⁹ substituents are geminally located on the same carbon R⁷ is not H and the geminally located OR⁷ or NR⁸R⁹ substituents can be taken together to form a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR⁸R⁹, SO₂R⁷, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-

oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3 - C_{10} cycloalkyl ring, a C_3 - C_{10} cycloalkenyl ring or a heterocycloalkyl ring;
aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, halogen, C_1 - C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , NR^8R^9 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, $COOR^7$, CN , $SO_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C_3 - C_{10} cycloalkyl ring, a C_3 - C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, CN , $COOR^7$, $SO_2NR^8R^9$, and SO_2R^7 ;

R^6 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_4 alkenyl, aryl(C_1 - C_6)alkyl, heteroaryl(C_1 - C_6)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C_1 - C_6 haloalkyl, OR^{13} , NR^8R^9 , C_1 - C_6 alkyl- OR^{13} , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, $COOR^7$, CN , $SO_2NR^8R^9$, and SO_2R^7 ;

R^7 is independently selected at each occurrence from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_3 haloalkyl, or heterocycloalkyl, C_1 - C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1 - C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1 - C_6 arylalkyl or C_1 - C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C_1 - C_6 haloalkyl, OR^{13} , NR^8R^9 , C_1 - C_6 alkyl- OR^{13} , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, $COOR^{13}$, CN , $SO_2NR^8R^9$, and SO_2R^{13} , with the proviso that when R^7 is SO_2R^{13} , R^{13} cannot be H

R^8 and R^9 are independently selected at each occurrence from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_2 -

C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each of which is optionally substituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;

R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H; and

R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN

with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to selectively inhibit binding of NPY peptides to NPY₁ receptors in vitro.